DETAILED DESCRIPTION

[Detailed Description of the Invention]

[0001]

[Field of the Invention]This invention relates to the hollow fiber for blood purification, and hollow fiber type artificial kidney used for a blood purification therapy especially a hemodialysis therapy, and hemofiltration dialysis. In more detail, while preventing invasion of the endotoxin from the dialysing fluid side, it is related with the hollow fiber for blood purification, and hollow fiber type artificial kidney which suppressed adsorption of blood platelets in the blood contacting surface.

[0002]

[Description of the Prior Art]Various artificial kidneys which used the present hollow fiber for the renal failure therapy are used. In recent years, it is shown that removal of with a molecular weights of 10,000 or more which made beta 2-microglobulin one index low-molecular-weight protein is effective in a therapy, and development of the blood purification film which has a fine hole which can pass low-molecular-weight protein has been performed briskly. In order to remove low-molecular-weight protein positively, simultaneous hemofiltration dialysis which combined hemodialysis and hemofiltration is performed.

[0003]However, since the dialysing fluid which flows through an opposite hand on both sides of a film flows into the blood side in the case of the above-mentioned therapy, If the size (pore size) of the membranous fine hole is expanded in order to remove low-molecular-weight protein, a possibility that the endotoxin (endotoxin) contained in dialysing fluid will invade into the blood side increases, and we are anxious about causing side effects, such as generation of heat.

[0004]Endotoxin has a hydrophobic part and it is known that it will be easy to stick to a hydrophobic material.

The endotoxin removal filter using this principle is developed.

JP,H10-151196,A and JP,H10-118472,A produce a hollow fiber only from hydrophobic Polymer Division, and are making endotoxin adsorb. In order to make the water penetration performance degradation by hydrophobic Polymer Division being furthermore apt to adsorb protein in blood improve, hydrophilic giant molecules are made to adhere only to a hollow filament inner surface. In these applications, a film production undiluted solution is not made to mix hydrophilic giant molecules, but hydrophilization treatment of the internal surface is carried out after film production noting that hydrophobing of a film outside surface is impossible, if hydrophilic giant molecules exist in a film production undiluted solution.

[0005]By a Prior art, specifying the suitable range was not shown by giving hydrophilic giant molecules to the hollow fiber which consists of hydrophobic Polymer Division, taking adjustment with the fall of the adsorption capability of the endotoxin by that water penetration performance improves and the hydrophilic nature of a hollow fiber increasing.

[0006]After adding hydrophilic giant molecules to the film production undiluted solution of hydrophobic Polymer Division and producing a film to it, when decreasing the quantity of the hydrophilic giant molecules of an outside surface by washing etc., the hydrophilic quantity molecular weight of the surface in contact with blood also decreases, and it is indicated to JP,H6-296686,A that adhesion of blood platelets etc. arise.

[0007]

[Problem(s) to be Solved by the Invention]In the hollow fiber produced from the film production undiluted solution with which the hydrophilic giant molecules which solved the above-mentioned problem, and hydrophobic Polymer Division were mixed, the purpose of this invention is to provide the hollow fiber for blood purification, and hollow fiber type artificial kidney which adsorbs endotoxin to an outside surface.

[0008]Furthermore, the purpose of this invention has the hydrophilic giant molecules in a hollow fiber in providing the hollow fiber for blood purification, and hollow fiber type artificial kidney to which blood platelets are not made to stick few.

[0009]

[Means for Solving the Problem]Many above-mentioned purposes are attained by the following hollow fiber for blood purification, and hollow fiber type artificial kidneys of this invention.

[0010](1) A hollow fiber for blood purification characterized by a ratio of hydrophilic giant molecules to hydrophobic Polymer Division in an outside surface of this hollow fiber being 5 to 25% in a hollow fiber manufactured from a film production undiluted solution which made the common solvent carry out dissolution mixing of hydrophilic giant molecules and hydrophobic Polymer Division.

[0011](2) A hollow fiber for blood purification given in (1), wherein said hydrophobic Polymer Division is polysulfone system resin.

[0012](3) (1), wherein said hydrophilic giant molecules are chosen from a group which consists

of a polyvinyl pyrrolidone, a polyethylene glycol and its copolymer, a polypropylene glycol, and its copolymer, or a hollow fiber for blood purification given in (2).

[0013](4) A claim (1), wherein an internal surface of said hollow fiber is coated with an antithrombotic compound thru/or a hollow fiber for blood purification given in (3).

[0014](5) (1), wherein said antithrombotic compound is vitamin E thru/or a hollow fiber for blood purification given in (4).

[0015](6) A hollow fiber type artificial kidney which has the hollow fiber indicated to the above (1) thru/or (5).

[0016]

[Embodiment of the Invention]This invention is explained in detail below.

[0017]Polymethylmethacrylate, polystyrene, polysulfone, cellulose triacetate, polycarbonate, polyarylate, etc. are mentioned, and hydrophobic Polymer Division which forms the hollow fiber for blood purification of this invention may be used combining these independence or two sorts or more. These hydrophobic Polymer Division can prevent the invasion by the side of the blood of the endotoxin from the dialysing fluid side, when it has endotoxin adsorptivity and it is used as an artificial kidney.

[0018]The hollow fiber for blood purification of this invention receives fixed washing processing in the film production undiluted solution after film production including hydrophilic giant molecules, and remains in a hollow fiber. The hydrophilic giant molecules used for this invention contain the copolymer containing polymers, such as polyvinyl alcohol, a polyethylene glycol, a polypropylene glycol, a polyvinyl pyrrolidone, and polytetramethylene oxide, or these. A polyvinyl pyrrolidone is preferably preferred in respect of the ease of film production nature and aperture control. 5 million dalton of desirable weight average molecular weight is 30,000 to 2 million dalton more preferably from 10,000. The aperture control for making it function as permeable membrane is easy.

[0019]5 to 25% of the ratio to hydrophobic Polymer Division of the hydrophilic giant molecules by the side of the dialysing fluid which remains in the hollow fiber for blood purification of this invention (usually outside surface of a hollow fiber) is desirable. If it is this range, the endotoxin contained in dialysing fluid can be made to adsorb effectively. It is 5 to 20% more preferably. The ratio to hydrophobic Polymer Division of the hydrophilic giant molecules by the side of dialysing fluid says the rate of an abundance ratio of these hydrophilic giant molecules and this hydrophobic Polymer Division measured with measuring methods, such as X-ray photoelectron spectroscopy (X-ray photoelectron spectroscopy, XPS), infrared spectroscopy, and a nuclear magnetic resonance method. For example, when polysulfone resin (PS) is chosen as hydrophobic Polymer Division and a polyvinyl pyrrolidone (PVP) is chosen as hydrophilic giant molecules, by XPS. From sulfur (PS), the elemental ratio of nitrogen (PVP), and the repeating unit molecular weight of PS and PVP which are a characteristic element, the

ratio of the total atomic weight of PS which exists in the hollow fiber surface, and each PVP can be computed and calculated.

[0020]As for the ratio of the hydrophilic giant molecules to hydrophobic Polymer Division of the whole hollow fiber of this invention, 1.0 to 6.0 % of the weight is preferred. It is 2.0 to 5.0 % of the weight more preferably. Washing operation must be performed superfluously and it is inefficient at below a lower limit. Above upper limit, the ratio of hydrophilic giant molecules will rise rapidly toward the inside of a film from a hollow fiber outside surface, the field to which endotoxin sticks decreases, and it is not desirable. The ratio of the hydrophilic giant molecules of the whole hollow fiber has the method of dissolving a hollow fiber in a solvent and analyzing by NMR etc., a method by ultimate analysis, etc. For example, when polysulfone is used as hydrophobic Polymer Division and a polyvinyl pyrrolidone is used as hydrophilic giant molecules, a weight ratio can be calculated from nitrogen by ultimate analysis, a sulphuric elemental ratio, and the molecular weight of the repeating unit of each Polymer Division.

[0021]When producing a hollow fiber, the wet spinning method or dryness-and-moisture type spinning method used conventionally can be used. When performing these spinning methods, said hydrophobic Polymer Division and hydrophilic giant molecules are dissolved in these common solvents, and a film production undiluted solution is adjusted. As this common solvent, although solvents, such as N,N-dimethylacetamide, N.N-dimethylformamide, N-methyl pyrrolidone, and dimethyl sulfoxide, are highly preferred for solubility, it is not limited to these, and two or more sorts of solvents may be mixed, and it may use. It is a point of the ease of acquisition preferably and N,N-dimethylacetamide and N.N-dimethylformamide are used independently.

[0022]In order to tune viscosity regulation, aperture control, etc. finely to a film production undiluted solution, a proper quantity of alcohol, glycerin, water, etc. may be added. The point of effluent processing to water is preferred, and 0.1 to 5 % of the weight is preferred to the above-mentioned fine adjustment in a film production undiluted solution.

[0023]When too low, film strength is small, and the concentration of hydrophobic Polymer Division in a film production undiluted solution must perform spinning work and assembly operation carefully, and is inefficient. If concentration is too high, the viscosity of a film production undiluted solution will rise, a film becomes precise, and the conditioning of the required aperture **** sake as an artificial kidney is difficult. When polysulfone is used as hydrophobic Polymer Division, the concentration in the film production undiluted solution of desirable hydrophobic Polymer Division is 15 to 19 % of the weight still more preferably 25% of the weight in 12 preferably 30% of the weight from 10. In detail, since a desirable density range is changed with the kind of hydrophobic Polymer Division, a molecular weight, etc., it is not limited to this range.

[0024]If the concentration of the hydrophilic giant molecules in a film production undiluted

solution is too low, good aperture control will become difficult, if too high, the viscosity of a film production undiluted solution will rise and spinning nature will get worse. When a polyvinyl pyrrolidone with a weight average molecular weight of 45,000 dalton is used as hydrophilic giant molecules, the concentration in a desirable film production undiluted solution is 7 to 10 % of the weight more preferably 15% of the weight from 5. Concentration low when what has a high molecular weight is used may be sufficient, and high concentration is preferred when what has a low molecular weight is used.

[0025]In the case of wet spinning or dryness-and-moisture type spinning, the mixture of the above-mentioned common solvent and water is mainly used as internal liquid which carries out the regurgitation from the inner tube of a double pipe nozzle. What mixed two or more sorts of above-mentioned common solvents for control of the coagulation speed of a film production undiluted solution, and other fluids may be mixed.

[0026]The film production undiluted solution breathed out from the double pipe nozzle is immersed in the coagulation bath which made water the subject. a film production undiluted solution -- a coagulation bath -- as a hollow fiber -- firmly -- form attachment ****. Then, if needed, it is immersed in a wash bath and rinses. PVP of an outside surface is washed, so that the temperature of a wash bath is high. In order to adjust PVP of the outside surface of a hollow fiber into a desirable ratio, it is preferred that the temperature of a wash bath shall be 40 to 80 **. It is preferred to wash especially at 50 to 70 **. Since it is [washing efficiency] higher to move the circumference of a hollow fiber, the wash water of this wash bath circulates wash water, and may be used. Under the present circumstances, since the PVP concentration in wash water becomes high gradually and washing efficiency falls during circulation, it is preferred to supply always new wash water. It is preferred that the quantity of the new wash water supplied in 1 hour is 10 to 50 of a wash water total amount%.

[0027]The hollow fiber washed by the wash bath can wash PVP of a hollow fiber outside surface positively by performing rolling up and washing with the mixed solution of warm water, alcohol, alcohol, and water, etc. further. Thus, the endotoxin adsorption capacity to an outside surface is obtained by making preferably the rate of an abundance ratio of the hydrophilic giant molecules of the outside surface of the obtained hollow fiber into 5 to 20% 25% from 5. Water permeability decreases that the rate of an outside-surface abundance ratio of hydrophilic giant molecules is less than 5%. If the rate of an outside-surface abundance ratio of hydrophilic giant molecules exceeds 25%, the hydrophilic nature of an outside surface will become high and the adsorption capacity of endotoxin will fall.

[0028]As for the hollow fiber for blood purification of this invention, it is preferred to give an antithrombotic compound in order to control blood platelet adhesion of the hollow filament internal surface in contact with blood. It is because the rate of an abundance ratio of the hydrophilic giant molecules of an internal surface also falls and blood platelets adhere easily,

when the rate of an abundance ratio of the hydrophilic giant molecules of a hollow fiber outside surface is made into 5 to 25%. With an antithrombotic compound, a styrene hydroxyethyl methacrylate copolymer, The polymeric material which has the hydrophilic portion and hydrophobic part like a polymer of the acrylic acid series monomer which has a hydrophilic group (meta), and the acrylic acid series monomer which has a hydrophobic group (meta), Fat soluble vitamins, such as long chain unsaturated fatty acid, such as eicosapentaenoic acid and docosahexaenoic acid, and vitamin E, are mentioned. The point that the stability to the ease and heat of processing is high to vitamin E is preferred. As vitamin E, alpha-tocopherol, beta-tocopherol, gamma-tocopherol, delta-tocopherol, alpha-tocopherol acetate, alpha-tocopherol nicotinate, etc. are mentioned.

[0029](Working example 1) The uniform dissolution of 19 % of the weight of polysulfones (P-1700), 9 % of the weight of polyvinyl pyrrolidones (K-30), and 72 % of the weight of the N.N-dimethylformamide was carried out, and the film production undiluted solution was adjusted. Internal liquid used 60 % of the weight of N.N-dimethylformamide, and the mixed liquor of 40 % of the weight of water.

[0030]An above-mentioned film production undiluted solution and internal liquid were simultaneously breathed out in the air from the outer tube and inner tube of the double tube regurgitation nozzle, respectively, and the coagulation bath with which water was filled was passed. After passing a coagulation bath, shower washing of the 60 ** warm water was carried out by a part for 1L/for 1 hour.

[0031]After shower washing, the hollow fiber was rolled round and it was made 10,000 bunches, and it processed underwater for 110 more ** 1 hour, and washed.

[0032](Working example 2) The uniform dissolution of 19 % of the weight of polysulfones (P-1700), 9 % of the weight of polyvinyl pyrrolidones (K-30), and 72 % of the weight of the N.N-dimethylformamide was carried out, and the film production undiluted solution was adjusted. 0.1% of the weight of alpha-tocopherol acetate and 0.1% of the weight of a polyethylene-glycols polypropylene-glycol copolymer (Pluronic F-68, Asahi Denka Kogyo K.K. make) were added and used for internal liquid to 60 % of the weight of N.N-dimethylformamide, and the mixed liquor of 40 % of the weight of water.

[0033]An above-mentioned film production undiluted solution and internal liquid were simultaneously breathed out in the air from the outer tube and inner tube of the double tube regurgitation nozzle, respectively, and the coagulation bath with which water was filled was passed. After passing a coagulation bath, shower washing of the 60 ** warm water was carried out by a part for 1L/for 1 hour.

[0034]After shower washing, the hollow fiber was rolled round and it was made 10,000 bunches, and it processed underwater for 110 more ** 1 hour, and washed.

[0035](Comparative example 1) The uniform dissolution of 19 % of the weight of polysulfones

(P-1700), 9 % of the weight of polyvinyl pyrrolidones (K-30), and 72 % of the weight of the N.N-dimethylformamide was carried out, and the film production undiluted solution was adjusted. internal liquid -- 60 % of the weight of N.N-dimethylformamide, and 40 % of the weight of water -- mixed liquor was carried out and it used.

[0036]An above-mentioned film production undiluted solution and internal liquid were simultaneously breathed out in the air from the outer tube and inner tube of the double tube regurgitation nozzle, respectively, and the coagulation bath with which water was filled was passed. After passing a coagulation bath, shower washing of the 60 ** warm water was carried out for 10 minutes by a part for 1L/.

[0037](Comparative example 2) The uniform dissolution of 19 % of the weight of polysulfones (P-1700), 1 % of the weight of polyvinyl pyrrolidones (K-30), and 80 % of the weight of the N.N-dimethylformamide was carried out, and the film production undiluted solution was adjusted. internal liquid -- 60 % of the weight of N.N-dimethylformamide, and 40 % of the weight of water -- mixed liquor was carried out and it used.

[0038]An above-mentioned film production undiluted solution and internal liquid were simultaneously breathed out in the air from the outer tube and inner tube of the double tube regurgitation nozzle, respectively, and the coagulation bath with which water was filled was passed. After passing a coagulation bath, shower washing of the 60 ** warm water was carried out by a part for 1L/for 1 hour.

[0039]After shower washing, the hollow fiber was rolled round and it was made 10,000 bunches, and it processed underwater for 110 more ** 1 hour, and washed.

[0040]The rate of an abundance ratio of the polyvinyl pyrrolidone of the outside surface of the hollow fiber obtained by working example 1 and 2 and the comparative examples 1 and 2 is measured by XPS, The hollow fiber type artificial kidney of effective membrane area ^{2} of 1.5 m was produced using the housing which has the inside of a hollow fiber, a blood inlet open for free passage, a blood outlet and a dialysing fluid entrance that is [outside surface side of a hollow fiber] open for free passage, and a dialysing fluid exit, and water penetration performance and endotoxin adsorption capacity were measured. A measurement result is shown in Table 1.

[0041]Using the above-mentioned hollow fiber type artificial kidney, measurement of water penetration performance returned Milli Q water by rate-of-flow 200 ml/min inside the hollow fiber, from the outside surface of the hollow fiber, was filtered by rate-of-flow 15 ml/min, and measured and computed the transmembrane pressure power difference at that time.

[0042]Measurement of the adsorption capacity of endotoxin was performed using the above-mentioned hollow fiber type artificial kidney as follows. The dialysing fluid of endotoxin concentration 800 EU/L is sent by rate-of-flow 30 ml/min from a dialysing fluid entrance, The dialysing fluid which controlled the flow from a dialysing fluid exit to 5 ml/min using the pump,

filtered the dialysing fluid which contains endotoxin from the outside surface side of a hollow fiber to the inside positively for 4 hours, and was filtered from the outside of the hollow fiber in the inside of the hollow fiber was stored, and the endotoxin concentration of this reservoir liquid was measured. Test liquid was not recycled but circulated only to one way.

[0043]

[Table 1]

	膜全体のPVP比率(%)	PVP外表面比率(%)	透水性能(ml/mmHg・hr)	エンドトキシン濃度(EU／L)
実施例1	2．8	17	490	検出限界以下
実施例2	2．3	14	470	検出限界以下
比較例1	6．7	30	460	8
比較例2	0．8	3	20	検出限界以下

検出限界：1EU／L

[0044]As Table 1, working example 1 and 2 has water penetration performance equivalent to the comparative example 1, and has the adsorption capacity of endotoxin. On the other hand, as for the comparative example 1, endotoxin was detected by the reverse filtration of dialysing fluid of 4 hours to the blood side. As for the comparative example 2, although the endotoxin by the side of blood was not detected, the water penetration performance decreased prominent.

[0045](Working example 3) Hydroxyethyl methacrylate, Methyl methacrylate. And the random copolymer of butyl methacrylate. Polymer concentration was diluted with methanol for the 30% of polymer concentration methyl-isobutyl-ketone solution of the block copolymer (the ratios of the polymer 1 and 2 are the weight ratio 50:50 and the average molecular weight 35,000) of (the polymer 1) and polyperfluoro alkyl methacrylate (polymer 2) to 0.7%. After dipping this solution in PS film inner surface of working example 1, the solvent was removed by 50 ** desiccation, and polymer was coated on PS film.

[0046]The water penetration performance of the artificial kidney of effective membrane area ^{2} of 1.5 m was 320 ml/mmHg-hr in the obtained hollow fiber.

[0047](Aging of a platelet count) The mini module of membrane area ^{2} of 300 cm was produced using the hollow fiber obtained in working example 1, working example 2, and working example 3.

[0048]Twice many Nembutal eating-raw-food [as this] diluent 1 ml/kg was injected intravenously and anesthetized using the rabbit (weight of 2.7-3.3 kg). The rabbit was fixed to standing ways, the blood vessel of the neck condition pulse was secured, and it circulated for 2 hours, without connecting a circuit and a mini module and using an anticoagulant by blood stream QB=10 ml/min. Blood collecting was performed from the artery side blood collecting

port of a mini module, and aging of the platelet count was measured. The rate of change of blood platelets was amended with the hematocrit value (lower type).

[0049]

[Equation 1]

$$\text{血球変化率} = \frac{PL_t \times Ht_0}{PL_0 \times Ht_t} \times 100\%$$

PL_0：循環前の血球数、Ht_0：循環前のヘマトクリット値

PL_t：循環t時間の血球数、Ht_t：循環t時間のヘマトクリット値

[0050]A result is shown in Table 2.

[0051]

[Table 2]

時間(分)	実施例1	実施例2	実施例3
0	100	100	100
5	90.1	93.5	89.7
10	89.1	90.8	86.0
15	83.8	90.4	84.6
20	81.9	87.2	85.7
25	79.9	86.7	84.3
30	75.1	85.5	84.9
45	65.5	84.0	83.3
60	61.6	80.9	81.6
120	57.5	84.8	81.3

[0052](Measurement of the erythrocyte membrane MDA) The following operations were performed using the mini module of working example 1 of membrane area ^{2} of 600 cm, and working example 2.

[0053]First, priming of 50 ml of the sterilized mini modules was carried out by eating raw food, the mini module was filled up with 10U/ml heparinized blood, and it incubated at 37 ** for 6 hours. Then, blood was collected from the mini module and the red count was counted with the blood count machine (Sysmex SE9000 and TOA Medical Electronics Co., Ltd.) (red blood cell count). It is plasma skimming (3,000 rpm) about 1.8 ml (finishing [a red blood cell count]) of blood collected from the mini module. 15min and 4 ** removed plasma, it centrifuged by having made the red corpuscles which precipitated to 10mM PBS(pH 8.0)5.4ml suspended (3,000 rpm, 15min, 4 **), and PBS of supernatant liquid was removed and washed. After performing this washing operation a total of 3 times, PBS of supernatant liquid was removed, 5mMPBS (pH 8.0)5.4ml was added, and red corpuscles were hemolyzed.

[0054]The hemolyzed above-mentioned sample is centrifuged (10,000 rpm, 15min, 4 **), PBS of supernatant liquid is removed and red corpuscles are made to mix and hemolyze 2.5mMPBS(pH 8.0)5.4ml. Furthermore it centrifuged (10,000 rpm, 15min, 4 **), and

centrifuged by removing PBS of supernatant liquid and making red corpuscles mix and hemolyze 1.25mMPBS(pH 8.0)5.4ml (10,000 rpm, 15min, 4 **). Hemolysis by 1.25mMPBS, centrifugal separation, and washing operation are repeated a total of 5 times. After removing PBS of supernatant liquid finally, the whole quantity was doubled with 2 ml by 1.25mMPBS.

[0055]MDA (malondialdehyde) was measured by the TBA method by making into a sample erythrocyte membrane obtained by the above-mentioned preparation (peroxylipid Test Wako: made by Wako Pure Chemical Industries, Ltd.). An operation method is shown below.

[0056]A result is shown in Table 3.

[0057]

[Table 3]

赤血球過酸化脂質 (n=5)

	MDA nmol／10^{10}RBC
PRE	3．507
実施1	6．701
実施2	5．558

[0058]By coating the hollow fiber inner surface side with an antithrombotic compound shows that reduction in blood platelets can be controlled. When vitamin E is used, it turns out that the hyperoxidation of erythrocyte membrane lipid can be controlled.

[0059]

[Effect of the Invention]In the hollow fiber produced from the film production undiluted solution with which hydrophilic giant molecules and hydrophobic Polymer Division were mixed, this invention can obtain the hollow fiber for blood purification, and hollow fiber type artificial kidney which adsorbs endotoxin to an outside surface as explained above.

[0060]Furthermore, this invention can obtain the hollow fiber for blood purification, and hollow fiber type artificial kidney to which the hydrophilic giant molecules in a hollow fiber do not make blood platelets stick few.

[Translation done.]